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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WHITEMAN, BRIAN A	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 11/05/2002 13

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/731,941	ALLEN, JAMES M.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 February 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17 and 21-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17 and 21-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *12*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Non-Final Rejection

Claims 1-17 and 21-23 are pending examination.

Applicants' traversal, the amendment to claims 2-5 and 11-17, and the addition of claim 23 in paper no. 13 is acknowledged and considered.

Claim Objections

Claims 4 and 13 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 4 and 13 claim a heterologous promoter, which is broader than a virus-inducible heterologous promoter.

Applicants' traversal is not applicable to the objection for claims 4 and 13.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-17 and 21-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 1) A method of producing a mammalian cell for packaging of recombinant AAV (rAAV) vector, said method comprising the steps of: a) providing a mammalian cell which comprises a stably integrated AAV cap and AAV rep gene operably linked to a helper virus-inducible heterologous promoter, wherein said genes are stably

integrated into the cell's genome and wherein p5 promoter function has been replaced by the helper virus-inducible promoter; b) replication the cell of step a) to produce a population of cells; and c) introducing a helper virus to the population of cells of step b); d) wherein the cells exhibits helper-virus inducible expression of stable integrated AAV rep gene; 2) A mammalian cell for packaging of rAAV vector, said cell comprising a stably integrated AAV cap and AAV rep gene in operably linked to a helper virus-inducible heterologous promoter, wherein said genes are stably integrated into the cell's genome and wherein p5 promoter function has been replaced by the helper virus-inducible promoter and wherein said cell exhibits helper-virus-inducible expression of said stable integrated AAV rep gene, and does not reasonably provide enablement for full scope of the claimed embodiment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claimed invention is directed to producing a cell for producing recombinant AAV vectors for use in gene therapy protocols.

The specification contemplates production of a mammalian cell comprising stably integrated AAV rep and cap gene operably linked to a heterologous promoter, wherein p5 promoter function has been replaced by said promoter (pages 34-48). The as-filed specification defines "stable integration" of a polynucleotide into a cell means that the polynucleotide has been introduced into a chromosome or mini-chromosome of a mammalian cell and therefore becomes a relatively part of the cellular genome (page 23). In addition, the specification only

produces a plasmid comprising AAV rep gene and AAV cap gene operably linked to the same heterologous promoter (Figure 1).

In view of the In re Wands Factors with respect to claims 1-17 and 21-23, the as-filed specification only provides sufficient guidance for 1)-2) listed above under scope of enablement because the as-filed specification does not provide sufficient guidance for one skilled in the art to make and/or use the full scope of the claimed embodiment. More specifically, the claims read on producing a mammalian cell line comprising a stably integrated AAV rep and a stably integrated cap gene, which encompasses genetic material carried episomally or stably integrated into the mammalian cell's genome. The specification states that, "episome plasmid can sometimes be maintained for many generations and genetic material carried episomally is generally susceptible to loss than chromosomally-integrated material" (pages 14, line 31-page 15, line 11 and page 23). Therefore, if the cap and rep gene are carried episomally the genes will be loss over time and will not be stably integrated in said cells. Thus as-filed specification only provides sufficient guidance for one skilled in the art to stably integrated said genes into the mammalian cell's genome.

Furthermore, the as-filed specification only provides sufficient guidance for one skilled in the art make a plasmid comprising AAV rep gene and AAV cap gene operably linked to the same heterologous promoter (page 27). The as-filed specification does not provide sufficient guidance for one skilled in the art to make and/or use two heterologous promoters in the claimed invention, wherein the cap gene is operably linked to a distinct heterologous promoter than the promoter operably linked the AAV rep gene. The specification cites several articles displaying the state of the art for the difficulty of producing a cell for efficiently producing AAV mainly

due to the activities of Rep protein (pages 5-16). In view of the state of the art cited by the specification, it is not apparent how one skilled in the art can use a heterologous promoter to control the expression of cap, while using a different promoter (virus-inducible promoter) to control rep expression if both genes are stably integrated into a cell's genome because when the rep gene is expressed the cap gene might not be expressed because it is under control of a different promoter and vice versa. The rep and cap genes are both required to produce rAAV and if both were not expressed then it would take one skilled in the art an undue amount of experimentation to produce rAAV. Therefore the full breadth of the claimed invention is not enabled in view of the lack of guidance provided by the specification. Thus, it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from using one heterologous promoter operably linked to said cap and rep gene to the full scope of the claimed invention. Therefore, the as-filed specification only teaches one skilled in the art how to make and/or use a plasmid comprising an AAV cap and an AAV rep gene in operably linked to a helper virus-inducible heterologous promoter.

In conclusion, the as-filed specification and claims coupled with the state of the art at the time the invention was made only provide sufficient guidance and/or evidence to reasonably enable the claimed invention for 1-2) listed above. Given the breadth of the term "stably integrated" and the unpredictability of using two distinct heterologous promoters, wherein the cap gene is operably linked to a distinct heterologous promoter than the promoter operably linked the AAV rep gene, one skilled in the art would have to engage in a large quantity of experimentation in order to practice the full scope of the claimed invention based on the applicant's disclosure and the breadth of the claims.

Applicants' traversal is not found persuasive for the rejection under 112 enablement because the traversal is not applicable to the rejection set forth above.

The rejections under 112 second paragraph are moot in view of the amendment to said claims. See pages 6-7.

The rejection under 102(e) for claims 1-17 and 21-22 is moot because Flotte does not teach claimed method. More specifically, the step of: replicating the cell of step (a) to produce a population of cells.

The rejection for claims 1-17 and 21-22 under 35 U.S.C. 103(a) are moot in view applicants' traversal and for the reasons set forth under 102. See pages 9-13.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, primary examiner, Dave Nguyen can be reached at (703) 305-2024.

If attempts to reach the primary examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader, SPE - Art Unit 1635, can be reached at (703) 308-0447.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal

Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

DAVE T. NGUYEN
PRIMARY EXAMINER

Brian Whiteman
Patent Examiner, Group 1635
11/4/02